Risk Factors for Cholinesterase and Non-cholinesterase Effects of Exposure to Organophosphate Insecticides in California Agricultural Workers: 1982-1990

Michael O'Malley, M.D.
Mary-Lou Verder-Carlos, D.V.M.
Louise Mehler, M.D.
Don Richmond

September 27, 1994

HS-1688

California Department of Pesticide Regulation
Worker Health and Safety Branch
1220 N Street, Sacramento, California 95814

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
1020 N STREET, ROOM 200, SACRAMENTO, CALFORNIA 95814

Abstract

Prior efforts to evaluate the comparative risk of organophosphate (OP) compounds have used numerator illness data from California's Pesticide Illness Surveillance Program (PISP) with corresponding pesticide use information to calculate illness/pesticide use ratios (IPURs). We present here a means of evaluating the comparative risk of organophosphate (OP) compounds, employing a standard epidemiologic technique known as a case-control study to calculate odds ratios (OR) associated with individual OP compounds. The study population consisted of 396 cases of illness related to cholinesterase (ChE) inhibition among California agricultural workers and 758 comparison subjects derived from PISP. The study subjects were similar to the California agricultural population as a whole in terms of age, gender, and ethnicity and the 30 Standard Industrial Classification (SIC) codes represented by study subjects accounted for 95% of the state's agricultural employment. The number of study subjects for each of the 36 compounds represented among study subjects also showed a significant correlation with the corresponding number of reported pesticide applications (Rank correlation=0.76, $p<0.001$). The cases and comparison subjects differed chiefly in respect to the presence or absence of cholinesterase inhibition (definitely or probably present among the case group and definitely absent among the controls). Approximately 72% of the controls had nonspecific symptoms that could conceivably have been due to exposure to a cholinesterase inhibiting compound but had cholinesterase values within the normal population range. The remaining cases involved respiratory and ocular irritation, and some were demonstrably related to other specific medical diagnoses. The individual compound most frequently associated with exposure to both case and control subjects was mevinphos (158 cases [39.9%] and 337 controls [43.9%]. Other compounds accounting for 10 or more case subjects included oxydemeton-methyl, parathion, phosalone, dimethoate, methamidophos, diazinon, chlorpyrifos, azinphos-methyl, methidathion, demeton, and (as a co-exposure) the carbamate compound methomyl. The exposure factors identified as significant in the crude analysis included application work and field residue exposure. Exposure to multiple category 1 OPs and multiple ChE inhibitors, and several individual compounds proved significant risk factors in stratified analysis. These included phosalone, methomyl, oxydemeton-methyl, and mevinphos. For the application associated ChE-illnesses exposures to mevinphos (OR=6.2) and multiple ChE-inhibitors (OR=2.9) remained significant in the multivariate analysis. Based on the limitations of the cholinesterase assays without baseline values, some misclassification of illness among control subjects actually related to ChE inhibition was possible. The study was also limited by lack of a population-based control sample. However, neither random nor non-random bias was likely to have accounted for the increased risk associated with application work and exposure to mevinphos observed in the study. This study demonstrated that registry based case-comparison analysis can provide a useful alternative to the IPUR as a means of evaluating the comparative risk of OP compounds, allowing simultaneous examination of demographic factors, work tasks, and multiple insecticide exposures.

Introduction

Illnesses associated with organophosphate (OP) compounds are among the classic hazards of agricultural employment.[1] Prior efforts to evaluate the comparative risk of organophosphate (OP) compounds have used numerator illness data from California's Pesticide Illness Surveillance Program (PISP) with corresponding pesticide use information to calculate illness/pesticide use ratios (IPURs).[2] This approach is problematic, because the number of individuals exposed - particularly those not directly involved in application work - may vary each time a pesticide is used. It is also unclear whether one should adapt the number of applications, or the pounds of pesticide applied, or the amount of pesticide sold, as a surrogate for the number of exposed individuals or person-hours of exposure. Further problems are introduced by variations in the collection and reporting of data. In 1990, 100% use reporting was begun in California, but in prior years reporting was required only for those pesticides designated as restricted use materials or applied by licensed pest-control operators (PCO's). Various reports employing use data in place of number of exposed persons have solved the dilemmas posed by these data in widely disparate manners.[3,4,5]

We present here an alternate means of evaluating the comparative risk for OP compounds, employing a standard epidemiologic technique known as a case-control[a] study.[6,7,8] This approach is possible because the spectrum of illness reports following exposure to OP compounds includes cases related to odor, cases related to respiratory and ocular irritation,[9,10] and occasionally cases that are demonstrably related to other specific medical diagnoses.[11,12] In drawing both case and control subjects from a common source, an illness registry of subjects exposed to pesticides, our study resembled previous studies of hospitalized cases and hospitalized controls involving such diverse illness endpoints such as cancer of the pancreas[13] and spontaneous abortion.[14] It most directly resembled recent cancer studies with cases and controls both drawn from cancer registries.[15,16,17,18,19] As controls, our study employed subjects with suspected systemic illness following OP exposure who were subsequently shown not to have ChE depression. This was in place of a hypothetical control group based upon an exposure survey conducted on a random sample of the California agricultural workforce (akin to those conducted in the non-agricultural sectors of the U.S. workforce by the National Institute for Occupational Safety and Health in both the 1970's[20] and 1980's[21]). Because the study measured the proportion of subjects with ChE illness following exposure to OP compounds, the calculated odds ratios (ORs) should be considered as analogous to proportionate morbidity (or more commonly, mortality) ratios (PMRs).[22,23] To the extent that the distribution of

---

[a] Cases are the ChE-related illnesses resulting from OP exposures and controls the non-ChE illnesses. These are taken to be representative of the general population exposures to OPs.

	ChE-Ill	**non-ChE ill**
Exposed	a	b
Non-exposed	c	d

The relative risk, or rate ratio (RR) for an exposure factor is computed as RR=[a/(a+b)]/[c/(c+d)], where b and d represent the entire non-ill population in the group of interest (e.g. applicators) and the comparison group, respectively. When the entire non-ill population cannot be determined, a proportionate morbidity ratio (PMR) can be computed using the same formula as the rate ratio. In this case, a and c represent the groups to which an event of interest has occurred (e.g. ChE-illness), and b and d represent the groups that experienced an event (e.g. non-ChE illness) but not the event of interest. Miettinen (Miettinen and Wang. An Alternative to the Proportionate Mortality Ratio. **American Journal of Epidemiology** 1981 114:144-148) observed that in this situation, the odds ratio (OR)=(ad/bc) is a more reasonable approximation to the rate ratio than the PMR.

exposures in the control group of non-ChE illnesses resembles the distribution of exposures to individual OP compounds in the underlying population of agricultural workers, the ORs may approximate the true population relative risk (RR).[24] Like other proportionate illness (or mortality) studies, it should be considered descriptive rather than analytical in nature because the uncertainty about the validity of this assumption that cannot be resolved without an external control population.

Methods

We reviewed 1,716 reports of suspected systemic OP poisoning in agricultural workers received by the California pesticide illness registry during the years 1982 to 1990. Each report involved at least one OP compound. Reports involving carbamate ChE inhibitors were not included in the review except where the compound was used with one or more OPs. The review focused on differentiating subjects with definite evidence of ChE inhibition and compatible symptoms (case subjects) from those who had normal reported ChE activity (control subjects). We excluded subjects whose ChE activity could not be determined from the registry files and those with definite sdepression of ChE activity and no symptoms compatible with ChE illness. The effect of the study subject selection and exclusion was systematically evaluated by comparing the demographic and employment profiles of cases, controls, and excluded subjects with values reported for the general agricultural population. We also compared the pesticides associated with the 1,716 reported episodes with those identified by California's 100% agricultural pesticide use reporting system.[25] The frequency of mucocutaneous irritation and the reported presence of chemical odor were also tabulated to evaluate whether the presence of these non-systemic effects differed among the cases, controls and excluded subjects.

Our method of reviewing individual reported exposures was similar to that used in previous registry reports on case series for individual OP compounds.[26] Reports were extracted from the PISP source file on finding an OP in one or more of the pesticide identification fields in the source file. Illnesses originally classified as unrelated to pesticide exposure were also reviewed to identify individuals who were part of illness clusters involving suspected exposure to OPs.

Review involved manual scrutiny of PISP files. The files included pesticide episode investigation reports (PEIRs), doctors' first reports of work related illness or injury (DFRs), and pesticide illness reporting (PIRs) and priority investigation reports. We extracted from each report information on signs and symptoms of illness, exposure history, and ChE data, where present. The review focused on systemic illness, but included all members of groups exposed in cluster episodes of suspected systemic illness, whether they reported systemic symptoms, skin or eye injury, or sought medical evaluation in the absence of symptoms. Details of the classification of symptoms, ChE data, exposures, and ChE-illnesses are given in Appendix 1.

Selection of Case and Comparison Subjects

The case group was selected from the entire OP case file based on the occurrence of definite or probable illness and employment in an agricultural SIC code. For descriptive purposes, this group was termed the *ChE illness group*. The comparison, or control, group included all subjects from the OP case file employed in agriculture and classified as unlikely illness, unrelated illness, or asymptomatic without evidence of ChE depression. Also included in the comparison group were subjects who had symptoms compatible with ChE effect who had reported ChE activity within the normal population range reported by the testing lab. For descriptive purposes, this group was termed the non-ChE effect group. *Excluded subjects* included those for whom investigation revealed no evidence of exposure, subjects with reported depressed ChE activity but no symptoms compatible with ChE effect, subjects with no reported ChE test, and subjects with definite illness for whom the responsible OP compound was not identified in the file.

Coding of demographic and employment information

Besides information specifically related to work exposure and illness, we coded demographic variables not originally coded in the original PISP file. These included sex, age, and ethnic origin (based on Hispanic vs. non-Hispanic surname). Standard industrial classification (SIC) codes[27,28,29] were used to identify categories of employment [major industrial divisions, and major subdivisions of agriculture]. The demographic profiles (age, sex, and ethnicity) of cases, controls, and excluded subjects were compared systematically with values reported from the general California agricultural population. Comparison sources included both census data and employment based demographic surveys.[30,31,32,33,34,35,36]

The distribution of SIC categories represented by the cases, controls and excluded subjects was also evaluated to determine the percent of the total agricultural population represented in each group. Reported annual average employment for each agricultural SIC code was derived from data gathered from state unemployment insurance tax records and data for each year between 1982 and 1990 published by the U.S. Bureau of Labor Statistics.[37]

Pesticide use data

Pesticide use data based on 100% use reporting were available for only one year of the study period, 1990.[38] Because 100% reporting was required for both agricultural and professional structural pest control applications, agricultural use was calculated by subtracting the reported structural applications from the total reported applications. The pesticide use represented by the study population was evaluated by enumerating the compounds associated with the reports of suspected systemic poisoning for all study subjects. The number of applications represented by pesticides affecting cases, controls and excluded subjects were then summed separately and compared to total OP use during 1990.

Statistical analysis was also conducted to evaluate the correlation (Spearman rank correlation [R_{rank}]) between the total number of applications reported for each compound and the corresponding number of cases, controls, and total study subjects. This evaluation was also conducted for individual exposure strata.

Statistical methods

Outline of data analysis

Analysis of demographic variables to assess similarities between cases, controls and excluded subjects

- **Frequency** counts for each group by gender, ethnicity
- **Comparison** of mean ages

Representativeness of the control subjects

- **Evaluated** against SIC employment data
- **Evaluated** against pesticide use data

Analysis of clinical characteristics for cases, controls, and excluded subjects

- **Frequency** of specific, non-specific, and irritant symptoms, the recorded presence of odor, hospitalization, disability, and degree of reported ChE inhibition.

Calculation of crude odds ratios (OR)

- **Individual** work activities and chemical exposures.

Calculation of OR by exposure strata

- **Chemical** exposures within exposure strata to test for confounding (association of exposure to individual chemicals with high risk activities) and effect modification (variation in OR across exposure strata)
- **The frequency** of exposure clustering within each stratum was also tabulated in order to evaluate the independence of observations within individual exposure strata.
- **For strata** without significant clustering, logistic regression used to evaluate the effect of multiple exposure risk factors

Figure 1 - outline of data analysis

The SPSS/PC statistical analysis program[39] was used for analyzing the coded information by exposure and illness category. Demographic variables were first analyzed to evaluate similarities between cases, controls and excluded subjects by age, gender and ethnicity. Differences between cases, controls and excluded subjects were also recorded for clinical characteristics such as frequency of specific, nonspecific, and irritant symptoms, the recorded presence of odor, hospitalization, disability, and degree of reported ChE inhibition.

Following characterization of the study population, crude ORs were calculated for individual work activities and chemical exposures. ORs for chemical exposures within exposure strata were also calculated to test for confounding (association of exposure to individual chemicals with high risk activities) and effect modification (variation in OR across exposure strata). For these analyses, a Yates' P2 was used to evaluate statistical significance, unless an expected cell frequency was less than or equal to five. A two tailed Fisher's exact test was then used. For strata with minimal exposure clustering, stepwise logistic regression analysis by method of the likelihood ratios[40] was also used. The regression models included demographic variables as well as variables related to chemical exposure.

Results

Between 1982 and 1990, the PISP source file contained records for 25,019 suspected illnesses, including 4,125 reports of suspected systemic illness following exposure to one or more OP compounds. For the cases involving OP exposure, 4,042 records contained sufficient information to classify the relationship between exposure and illness (Figure 2) and 1,716 of these (42.5%) involved agricultural employment. The exposures related to agricultural employment included 401 subjects with ChE related illness; 5 of these subjects were excluded because the OP compound involved was unknown or not specified in the investigation. The *case group therefore included 396 subjects*. Of the 1,315 subjects without demonstrable ChE related illness, *758 (57.6%) met the criteria for inclusion as controls*.

This group included 550 subjects with nonspecific symptoms possibly compatible with ChE illness who had ChE values in the population normal range; 30 subjects who had symptoms compatible with ChE-related illness, but no change from baseline ChE activities (definite evidence of lack of ChE inhibition); 10 subjects who had unrelated medical diagnoses; 47 subjects who had one or more

Selection of Case and Control Subjects

25,019 suspected pesticide illnesses 1982-90

9

4,125 reports involving organophosphates (OPs)

9

4,042 reports with sufficient information to classify the illness-exposure relationship

9

1,716 subjects with agricultural employment

9

401 potential case subjects - **396** total case subjects; **5** excluded because OP compound was unidentified

\+

1,315 subjects without demonstrable ChE depression (potential controls)

9

758 met the criteria for controls; these included **550** subjects who had symptoms compatible with, but not specific for OP poisonings and ChE levels within the normal population range; **30** subjects without change from baseline ChE levels; **10** subjects with definitely unrelated medical diagnoses; **47** subjects with only irritant symptoms; and **121** subjects with confirmed exposure, but no reported symptoms.

\+

557 excluded subjects included **46** subjects with suspected poisoning who had no evidence of exposure on investigation, **26** with exposure to unknown OP compounds; **46** subjects with asymptomatic cholinesterase depression and an additional **3** subjects with ChE depression but only irritant symptoms, and **436** subjects with compatible symptoms but no reported information on ChE activity.

1,154 total study subjects - **396** cases and **758** controls - **562** total excluded subjects including 5 cases of ChE-related illness associated with unknown OP compound(s)

Figure 2 - Selection of cases and controls

irritant symptoms and no symptoms compatible with ChE related illness and no evidence of ChE depression; and 121 asymptomatic exposures who had no evidence of ChE depression. The total number of subjects meeting the criteria for inclusion in the study was thus 1,154.

Comparison between cases, controls, and excluded subjects with general population of agricultural workers

Demographic variables

Data in Table 1 show that the study population was predominantly male (81.1%), had Hispanic surnames (80.9%), and had a mean age of 30.9 years. Cases, controls, and excluded subjects showed small but statistically significant differences[b] from each other and from the values for the entire group for these same demographic variables. The values for the study subjects as a whole and for each subgroup were also similar to those reported for the agricultural population as a whole (Table 1 and Figure 3).

% of agricultural workforce represented by the study population

The 19 SIC categories represented by one or more case subjects accounted for 84.7% of the total agricultural employment (defined by annual average employment data collected from unemployment insurance rolls) during the study period (Appendix 2). The 21 SIC categories represented among the control subjects accounted for 87.8%, and the 30 SIC categories represented among the excluded subjects for 98.7% of the total employment. The 30 categories represented by at least one case or a control subject represented a total of 3,478,626 person-years of employment in the 9 years between 1982-1990 - 94.7% of the total person-years for all California agricultural employees during the same period (Appendix 2). Eight SIC categories or groupings not represented among the 1,154 study subjects included corn (SIC 0115), soybeans (SIC 0116), general crop services (0724), animal specialty services (0752), farm management services (0762), forestry (SIC group 08), and farming, fishing and trapping (SIC group 09). Together these categories accounted for 196,272 person-years of employment during 1982-1990, equal to 5.3% of the total person-years reported.

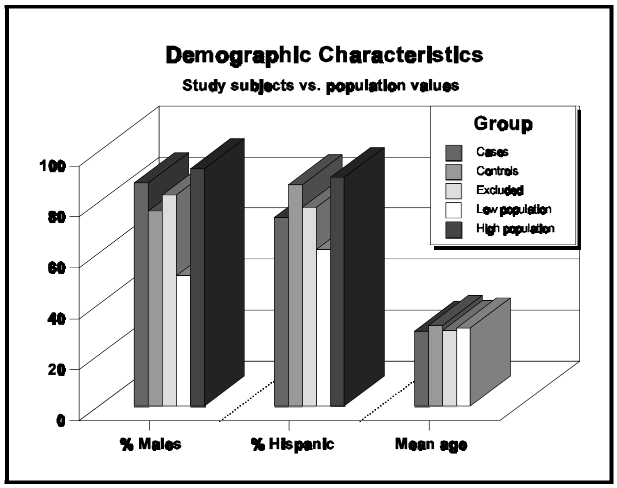

Figure 3 - demographic characteristics of cases, controls and excluded subjects versus low values (designated as *low population* in the graph) and high values (designated as *high population*) reported in published demographic studies of California's agricultural work force (single value available for mean age).

% of pesticide applications represented by reported exposures

The spectrum of pesticides to which study subjects had exposures (shown in Appendix 3) was evaluated by enumerating the compounds associated with the reports of suspected systemic poisoning for all study subjects and comparing the list to pesticide use reports. In 1990, the first year of 100% use reporting, 414,546 applications of 53 OP and carbamate pesticides were reported. The 33 compounds represented among case subjects, the 30 compounds represented among controls, and the 40 compounds represented among excluded cases accounted for over 99% of the OP/carbamate applications reported in California

[b] Each of the referenced values was statistically significant, $p<0.05$.

during 1990. The 17 compounds represented by neither case nor control subjects accounted for less than 2% of the total applications reported. Four of the 17 compounds not represented were carbamates (accounting for 3343 [69%] of the 4819 unrepresented applications), and may appear in the PISP database unaccompanied by OP exposure.

Statistical analysis showed significant[c] correlation ([R_{rank}]) between the total number of applications (unadjusted 1990 data used as a surrogate for the entire study period) reported for each compound in Appendix 3 and the corresponding number of cases (R_{rank}cases = 0.74), number of controls (R_{rank}controls = 0.80), and total number of study subjects (cases and controls, R_{rank}total = 0.76). For the individual exposure strata the following correlation values were observed: *Application exposure* - R_{rank}cases = 0.61, R_{rank}controls = 0.59, R_{rank}total = 0.76; *field residue exposure* - R_{rank}cases = 0.52, R_{rank}controls = 0.58, R_{rank}total = 0.55; and *drift exposure* - R_{rank}cases = 0.52, R_{rank}controls = 0.58, R_{rank}total = 0.58.

Symptoms, disability, and hospitalization

Differences among cases, controls, and excluded subjects for several important case characteristics are shown in Table 1 and illustrated in Figure 4. By definition case subjects were more likely than controls to have nonspecific symptoms (100%) compatible with ChE-related illness than the controls (75.9%) or excluded subjects (58.0%). Specific symptoms were by definition present in all of the probable cases and none of the controls or excluded cases. Among the 311 subjects with definite ChE-related illness, specific symptoms were found in 80 (25.7%). The reported presence of chemical odor was more likely to have been noted by control (48.8%) subjects than either case subjects (20.2%) or excluded (21.9%) subjects. Similarly control subjects (34.7%) were slightly more likely to report either respiratory, eye, or skin irritation than either case (28.8%) or excluded (29.4%) subjects. By contrast case subjects (69.2%) more often reported time lost from work following their illness than either control (42.6%) or excluded subjects (36.5%); cases also had a markedly greater likelihood of hospitalization (27.1%) than either controls (2.2%) or excluded subjects (8.2%). Cluster episodes accounted for 173 (43.7%) of the 396 case subjects and for 515 (67.8%) of the 758 controls.

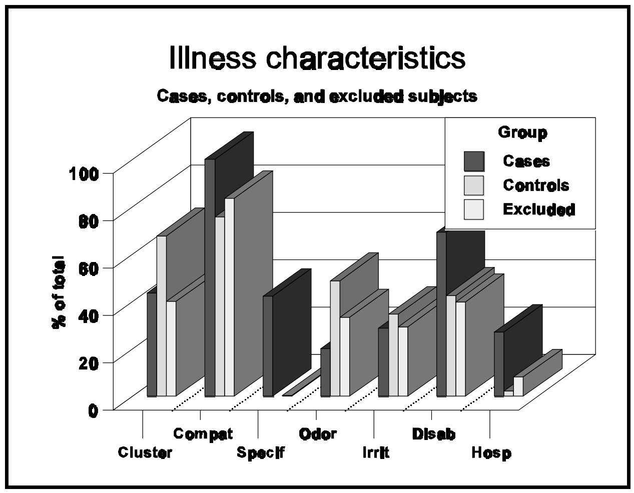

Figure 4 - illness characteristics: **cluster** - % of cases related to illness clusters; **compat** - compatible symptoms; **specif** - specific symptoms; **odor** - reported presence of odor; **irrit** - reported presence of irritation; **hosp** - hospitalization; **disab** - lost work time

ChE Activity

Comparable to the disparity in reported hospitalization, the case group differed markedly from the controls and excluded subjects by ChE activity. Table 2 and Figure 5 show the results of cholinesterase testing in the case, control and excluded groups. By definition, all subjects with ChE depression (either below the normal range or more than 20% below a baseline or follow-up test) were cases, unless excluded from analysis because of absence of compatible symptoms or lack of exposure information. The majority of the cases (234 of 396) were identified by ChE test results below the normal range. Another 26 were included

[c] Each of the referenced correlation coefficients is significant, $p<10^{-5}$.

as cases based on a statement that their ChE levels were reduced, although specific results were not provided, while 51 showed ChE depression compared with either a baseline or follow-up test. The remaining 85 cases had symptoms specific to ChE inhibition. No information on ChE level was available for 57 of the 85. The other 28 had test results in the normal range but no personal comparison values.

Of the 234 cases identified by cholinesterase results below the normal range, 11 provided only plasma cholinesterase results and only the lower limit of the normal range. These 11 cases ranged from the lower limit to 81% below the limit. Depression for the other 223 cases was calculated relative to the midpoint of the normal range, with a median of 47.6% depression for RBC and 59.1% for plasma. For the 42 cases with baseline results, median RBC depression was 48.8% and median plasma depression was 59.1%. The nine cases evaluated relative to follow-up tests had median RBC depression of 22% and median plasma depression of 20%.

Of the 758 controls, 653 subjects (86.1%) had ChE levels in the population normal range. Nineteen (2.5%) of the control subjects had baseline tests that indicated depression of less than 20%. Six (0.8%) of the control subjects had plasma ChE activity tested by a laboratory listing only the lower limit of normal on its reports; all had levels above the reference point.

Excluded subjects (n = 557) included 14 subjects (2.5%) whose ChE activity levels were reported normal**,** excluded because investigation revealed no evidence of exposure; 28 subjects with reported depressed ChE activity, excluded for being asymptomatic; 463 subjects (83.1%) with no reported ChE test; and 51 with depressed ChE but no compatible symptoms. One case (0.2%) with only plasma ChE and only the lower limit of the population range reported was excluded for being asymptomatic.

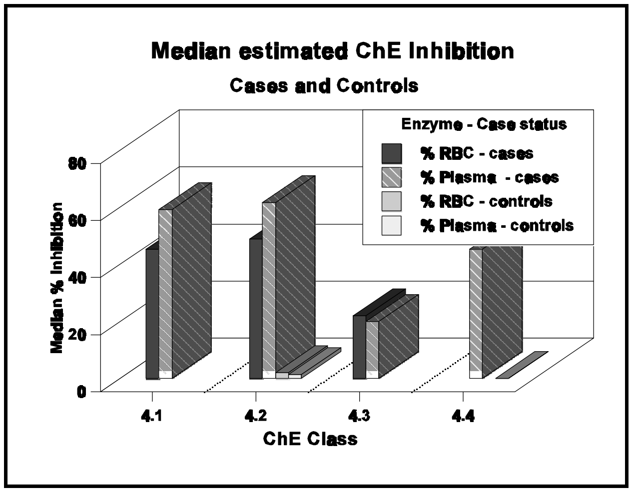

Figure 5 -ChE inhibition cases vs. controls by ChEclass: **4.1**=ChE depressed below lower limit of population normal, depression estimated from midpoint of normal range; **4.2**=ChE depression calculated from available baseline data; **4.3**=followup data used to estimate % depression; **4.4**=depression estimated from lower limit of normal because upper end of reference range not reported by test laboratory and only plasma test performed

Crude analysis for individual exposure related variables - Exposure categories (Work activities)

The 467 (40.5% of the total cases and controls) individuals with drift exposure accounted for the largest number of study subjects by exposure category. These were followed by the 356 (30.8%) subjects with application work, including 99 individuals with accidental direct exposure, 212 associated with reported application work and 45 associated with documented violations of proper application procedure. There were 266 (23.1%) subjects with field residue exposure, including 76 associated with violations of field reentry intervals, and 174 with associated with normal field reentry. The remaining 65 subjects with exposures in the miscellaneous category included six who had exposure resulting from accidental ingestion and additional subjects with exposures resulting from OP residues on commodities, pesticide fires, and exposure to OP concentrate (Table 3).

SIC categories were also related to exposure categories. Of the 445 workers in the agricultural services SIC group, 211 (47.4%) had application exposures, compared to 145 (20.5%) of the 709 remaining study subjects. Of the 218 subjects in SIC 0721 (crop protection services), 191 (87.6%) had application exposures. By contrast, drift exposures accounted for 301 (79.6%) of the 378 study subjects in SIC 0161 (vegetable and melon production), field residue exposures for 44 (11.6%), and application exposure accounted for only 28 study subjects (7.4%).

Case subjects (45.2%) were less likely than controls (69.4%) to work in crop production SICs and correspondingly more likely to work in agricultural services (Table 1). Excluded subjects (60.1%), like controls, were more likely than cases to work in crop production SICs. For individual SIC codes, cases were less likely than average to occur among vegetable and melon workers (0161), and more likely to occur among crop protection services workers (0721).

Application exposure

Application exposures appeared significantly less likely to occur in clusters than other types of exposure. The 356 application-associated exposures included only 25 (7%) that occurred in clusters of two or three. By contrast, cluster episodes accounted for 663 (83.1%) of the 798 subjects exposed other than in making applications (Figure 6).

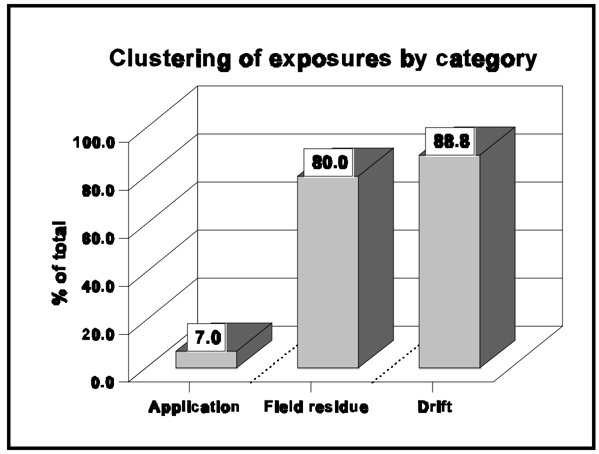

Figure 6 - clustering by exposure category

Subjects exposed while making applications also differed from the remainder of the subjects in being less likely to report odor (12.9% vs. 50.6%, $p < 10^{-5}$ by Yates' P2), less likely to report irritation symptoms (26.7% vs. 35.3%, $p = 4.7 \times 10^{-3}$ by Yates' P2), and more likely to experience recognizable ChE depression. The subjects with application associated OP exposures had a higher risk of ChE-related illnesses than subjects in the remaining exposure categories ($OR_{app} = 4.08$, $p < 10^{-5}$) and for SIC 0721 (crop protection services) the risk was slightly lower ($OR = 3.81$, $p < 10^{-5}$). Among the subcategories of application exposure, direct exposure ($OR_{direct} = 6.74$, $p < 10^{-5}$) and violations of normal application procedure ($OR_{viol} = 4.51$, $p = < 10^{-5}$) had risks higher than the application stratum as a whole. Subjects whose exposure resulted from normal application procedure ($OR = 1.81$, $p = 1.4 \times 10^{-4}$) had a lower comparative risk for ChE related illnesses than cases in the other application categories, but nonetheless significantly higher than the remaining study subjects (Figure 7).

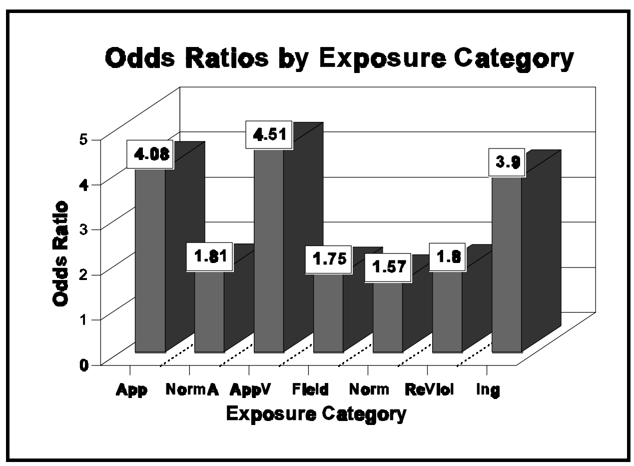

Figure 7 - summary of odds ratios for exposure categories - **App** (application exposure), **NormA** (routine application work), **AppV** (violation of proper application exposure); **Field** (field residue exposure), **NormF** (normal field reentry), **ReViol** (violation of field reentry interval), **Ing** (ingestion)

Among the application associated cases, neither age range nor sex was a significant predictor of case status ($p = .09$ by Pearson P2 for age range, and $p = 0.53$ for sex). Hispanics made up a lower percentage of the application cases (53.9%) than application controls (66.9%, $p = 1.9 \times 10^{-2}$).

Field residue exposure

The field residue exposures had a marked tendency to involve cluster illness episodes. Of the 275 field residue exposures that met study criteria, 220 (80.0%) resulted from one of 28 cluster episodes reported in the study period. The 14 episodes involving 4 or more reported exposed individuals (Table 4) accounted for 186 (84.5%) of the cluster associated exposures. These included noteworthy episodes of reentry violations (in fields treated with mevinphos and methomyl [index case id number 2095-82]). Several episodes also occurred despite compliance with the reentry intervals then in effect (parathion [index IDs 1523-82 and 1421-85] and phosalone [index IDs 1815-87, 1850-87, 1918-87, and 2162-87] without violation of the then existing reentry interval. Among the field residue associated cases neither age range nor ethnicity was a significant predictor of case status ($p = .053$ by Mantel-Haenszel P2 for age range, and $p = 0.053$ for ethnicity [Hispanic vs. non-Hispanic surname]). However, women made up a higher percentage of the field residue cases (85.6%) than the field residue controls (75.0%). This finding was of borderline statistical significance ($p = .047$ by Yates P2).

The 275 field residue exposures that met the study criteria had a significantly elevated frequency of definite-probable illness compared to the remaining exposure categories. However, the elevation was less marked than for exposures associated with application work ($OR_{field} = 1.75$, $p = 1.1 x 10^{-4}$). For field reentry violation episodes, the increased risk of ChE related illness was more marked ($OR_{viol} = 1.80$, $p = 1.9 x 10^{-2}$) than for cases associated with routine field work ($OR_{rout} = 1.57$, $p = 6.42 \ x 10^{-3}$). Odor was noted significantly less frequently in the PISP registry file for field residue associated exposures (22.0% of subjects) compared to other exposure categories (44.0% of subjects, $p < 10^{-5}$ by Yates' P2). Irritation symptoms were noted with approximately the same frequency among subjects with field residue exposure (30.1% of subjects) as with other types of exposure (33.4% of subjects, $p = .34$ by Yates' P2).

Drift exposure

The 470 study subjects with drift associated exposures had a significantly lower frequency of ChE related illness than subjects in the other exposure categories ($OR_{drift} = 0.12$, $p < 10^{-5}$). However, the drift exposures were more likely to be associated with both reported presence of odor (74.0% of drift exposures vs. 19.0% of other exposures, $p < 10^{-5}$ by Yates' P2) and symptoms of irritation (46.3% of drift exposures vs. 37.3% of other exposures, $p = 2.21 x 10^{-3}$) than subjects in other exposure categories. The drift exposure cases were not significantly associated with age range ($p = 0.50$ by Mantel-Haenszel O2), sex ($p = .78$, by Yates' P2), or ethnicity ($p = 0.77$ by Fisher's two-tailed exact test).

The drift exposures had a marked tendency to involve cluster illness episodes. Of the 467 drift exposures that met study criteria, 415 (88.8%) resulted from one of 29 cluster episodes reported in the study period. The 15 episodes involving 4 or more exposed individuals (Table 5) accounted for 390 (83.5%) of the cluster associated exposures. No individual chemical compound or category of mixtures was significantly associated with the 51 cases of cholinesterase related illness in the drift exposure category.

Ingestion

Four ChE-illnesses and two non-ChE illnesses resulting from accidental ingestion of OP insecticides were reported among the California agricultural workforce during the study period ($OR = 3.9$, $p = 0.19$ by Fisher's two-tailed exact test). These included 4 exposures resulting from ingestion of contaminated produce and 1 from drinking contaminated water from an irrigation canal. The remaining case involved the only fatality among the study subjects, an applicator who died during a dormant spray application of parathion. The autopsy showed several hundred parts-per-million (ppm) of parathion in the stomach, but because the exposure was not witnessed, the exact circumstances leading to the ingestion remain uncertain. Details of this case have been reported extensively elsewhere.[41,42]

Chemical exposures - crude and stratified analysis

The individual compound most frequently associated with exposure to both case and control subjects was mevinphos (158 cases [39.9%] and 337 controls [44.5%]). Other compounds accounting for 10 or more case subjects included methomyl, oxydemeton-methyl, parathion, phosalone, dimethoate, methamidophos, diazinon, chlorpyrifos, azinphos-methyl, methidathion, and demeton. Crude ORs for these exposures (Table 3) show that significantly increased risk of ChE-illness was present for methomyl ($OR = 1.48$, $p = 0.015$, by Yates' P2), phosalone ($OR = 10.04$, $p < 10^{-5}$ by Yates' P2), diazinon ($OR = 2.27$, $p = 1.55 \times 10^{-3}$ by Yates' P2), and demeton ($OR = 3.90$, $p = 0.017$, by Yates' P2). However, analysis by exposure strata (Table 4) showed the presence of both confounding (association of individual chemical exposures with particular exposure strata) and effect modification (variation in OR across exposure strata) within the data.

Application exposure (n = 356) - Individual compounds showing increased comparative risk following application exposure included mevinphos ($OR = 7.72$, $p < 10^{-5}$), methomyl ($OR = 3.8$, $p = 8 \times 10^{-5}$), and methamidophos ($OR = 3.09$ $p = 3.7 \times 10^{-2}$). A significant association was also noted for the redundant categories exposure to multiple category 1 ChE inhibitors ($OR = 4.40$, $p = 4.0 \times 10^{-4}$) and multiple ChE inhibitors ($OR = 3.25$, $p < 10^{-5}$). Significantly diminished risk was associated with application of acephate ($OR = 0.16$, $p = 7.6 \times 10^{-4}$) and parathion ($OR = 0.37$, $p = 3.7 \times 10^{-4}$).

Multiple ChE inhibitors, multiple category 1 OPs, methomyl, and methamidophos all showed significant positive association with the use of mevinphos. For example, of the 102 subjects with application exposures to mevinphos, 61.7% had exposure to multiple ChE inhibitors, compared to 24.4% of the remaining 254 subjects with application exposures; 30.3% involved multiple category 1 OP's compared to 4.3% of the 254 remaining subjects. When all application exposures (n = 356) were examined in a multivariate logistic analysis (Table 5 and Figure 8), elevated risk was associated with the demographic variable Hispanic surname ($OR = 1.8$, $p = 0.02$), with exposure to mevinphos ($OR = 6.2$, $p < 10^{-5}$), and with exposure to multiple ChE inhibitors ($OR = 2.1$, $p = 0.005$). Gender, exposures to methamidophos, methomyl, and exposures to multiple category 1 OPs were also examined in the model but did not prove significant.

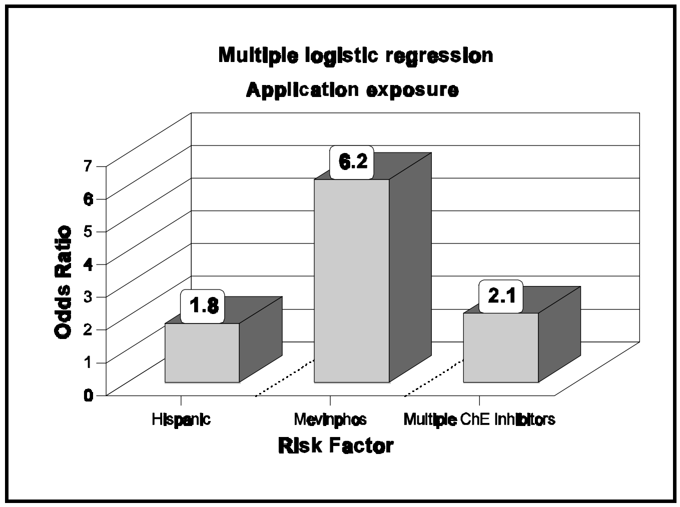

Figure 8 - Logistic regression analysis for application exposure cases (n=356). Gender, age, exposures to methamidophos, methomyl, and exposures to multiple category 1 OPs were also examined in the model.

Field residue exposure (n = 275) - Individual compounds significantly associated with ChE illness following field residue exposure included phosalone ($OR = 10.5$, $p < 10^{-5}$), mevinphos ($OR = 3.41$ $p = 5.2 \times 10^{-4}$), and oxydemeton-methyl ($OR = 1.88$, $p = 4.0 \times 10^{-2}$). A significant association was also noted for exposure to multiple category 1 ChE inhibitors ($OR = 8.81$, $p < 10^{-5}$). A significant negative association with definite-probable illness was also noted for exposures to acephate ($OR = 0.10$, $p = 4.5 \times 10^{-4}$), azinphos-methyl ($OR = 0.20$, $p = 3.5 \times 10^{-3}$), and dimethoate ($OR = 0.20$, $p = 9.7 \times 10^{-4}$). Because cluster exposures accounted for 80% of the subjects with field residue exposure, no multivariate analysis was done for this stratum.

Discussion

Both the ChE and non-ChE illness groups were broadly representative, within the limitations of the available demographic data, of the California agricultural workforce. Additionally, the compounds represented among the cases and controls accounted for more than 96% of the OP/carbamate applications made in the state and the SIC categories represented accounted for 87% of the state's agricultural employment. Statistical analysis showed significant correlation ([R_{rank}]) between the total number of applications and the corresponding number of cases (R_{rank}cases = 0.74), number of controls (R_{rank}controls = 0.80), and total number of study subjects (cases and controls, R_{rank}total = 0.76).

As noted in other literature,[43,44] OP exposures reported to the registry that did not result in ChE depression were accompanied (Table 1) by a high frequency of odor complaints (49%) and irritant symptoms (34.7%). Nevertheless, odor and irritation were also seen among case subjects, and 75.9% of the controls had nonspecific symptoms compatible with ChE-related illness. By definition specific symptoms and definite ChE inhibition were confined to the case group. In the approximately 67% of the cases for whom the degree of ChE inhibition could be estimated, the median depression was approximately 50% for RBC ChE and approximately 60% for plasma ChE; specific symptoms were present in 42.2% of the case group. Cases and controls differed most markedly in percentage of cases and controls who lost time from work (69.2% vs. 42.6%) or were hospitalized (27.1% vs. 2.1%). Neither of these findings could be considered inherently related to the study definitions.

Differential reporting bias

A differential bias in reporting of odor or irritation associated-illnesses for individual OP compounds could arise based on innate variations in the tendency of individual compounds to form mercaptan and di-sulfide byproducts with low odor thresholds. Mercaptan and di-sulfide levels associated with OP application have been reported for too few products to assess this possibility systematically. However studies of the cotton defoliants Def® (S,S,S-tributylphosphorothioate) and Folex®(S,S,S-tributylphosphothioate or merphos) indicate that parts-per-billion (ppb) butyl mercaptan levels are present following applications. Simultaneous measurements show concentration of the active ingredients fall well below the parts-per-trillion (ppt).[45,46] Ethyl mercaptans and di-ethyl sulfides may be present in a similar concentration following applications of chlorpyrifos.[47] For compounds such as dichlorvos and mevinphos with no sulfur moiety and high innate vapor pressures (10^{-3} mm Hg compared 10^{-5} to 10^{-9} mm Hg for other OP compounds[48]), the odor may be more likely to signify the presence of the active ChE inhibitor (or the presence of other OPs when either compound is used in a tank mix with thiophosphate insecticides). In this study, only 2 cases and 4 controls had reported exposure to dichlorvos, but mevinphos accounted for 39.9% of the cases and 43.7% of the control exposures and had greater than the median number of application control subjects (Appendix 4). However, the number of mevinphos application controls (2.8/10,000) was less than 50% of the median value (5.7). This might suggest under-reporting of non-ChE illnesses for mevinphos, but the total number of application study subjects/10,000 applications for mevinphos (20.4) was approximately 33% above the median value and the number of mevinphos-cases/10,000 applications was more than double the median value. These findings suggest that the elevated OR for mevinphos observed in this study was not attributable to a differential reporting bias, but rather the inherent properties of the compound - most notably its high vapor pressure and its high toxicity.

Odor and illness clusters

The association of odor and irritation symptoms with illness clusters observed in this study deserves some discussion. The most obvious explanation is that the presence of odor combined with symptoms of irritation is likely to provoke members of a group to seek medical treatment. An alternate possibility is that the presence of odor is more likely to be reported by subjects involved in cluster episodes or recorded more systematically by the field investigators than in episodes involving illness in a single subject. These considerations deserve some weight in evaluating the differential tendency of ChE and non-ChE related illness to occur in clusters. Group episodes accounted for 43.7% of the 396 case subjects and 67.5% of the 758 control subjects.

The differential tendency of cases and control subjects to cluster is probably a secondary effect of differential clustering by exposure categories. Cluster episodes accounted for 82.7% of the 220 field residue exposures that met the study criteria and for 88.9% of the 467 drift exposures. By contrast clusters accounted for only 7.0% of the 356 application related exposures. The differential clustering by exposure category has several important consequences. In terms of our study design, it means that neither the ChE-illnesses nor the non-ChE illnesses in the field residue and drift exposure strata are reported randomly. Although OR can be calculated for these strata, it may be most appropriate to consider individually the significance of the field residue clusters listed in Tables 6 and the clusters associated with drift exposure listed in Table 7. California regulatory policy has appropriately considered field residue clusters in this fashion and limited use of individual compounds such as parathion[49] (IDs 1421-82,1439-83, and 1450-85 in Table 6) and phosalone[50] (IDs 1815-87, 1850-87, and 1918-87 in Table 6), on hand harvested crops. This has recently resulted in decreased number of exposure clusters associated with routine field reentry, but exposures associated with reentry violations in hand harvested row crops (eg ID 2095-82 in table 6) have continued to occur.

In statistical terms, high frequency of clustering in the drift and field residue exposure strata, mean that the non-ChE illnesses in these strata are unlikely to be a good surrogate for a randomly chosen sample of the field worker population they represent. Furthermore, the presence of both effect modification (variation in OR across exposure strata for most OP compounds) and confounding (association of individual OP compounds with certain types of exposure) mean it is not appropriate to calculate either crude (Table 3) or adjusted ORs ratios for the entire data set. However, limitations imposed by the occurrence of clusters in the field and drift exposure strata do not apply to statistical evaluation of the ChE and non-ChE-illnesses associated with application exposures. While it cannot be ascertained from our study data how closely these subjects resemble a random sample of the underlying population of agricultural applicators, they are plausibly representative within the limitations of the available demographic data, derived principally from studying groups of harvesters and field laborers.

Random misclassification bias

A potential source of random misclassification bias in this study is the necessary reliance on single ChE levels for many of the control subjects. It has previously been demonstrated that in illness outbreaks (when a high prevalence of ChE illness is present) single ChE values in the normal population range have a poor negative predictive value.[51] Although routine agricultural employment involves intermittent contact with OP compounds for non-applicators,[52,53,54,55,56,57,58,59] some random misclassification of true ChE illnesses might have occurred in the control population. This potential bias would reduce the efficiency of the study and could explain some of the disability observed in the control population. It would not explain the observed statistical association between ChE illness and most individual exposure factors. Similarly the reduction in study efficiency produced by exclusion of 562 subjects was unlikely to have produced non-differential misclassification bias that would explain the major findings of this study, e.g. the association of ChE-related-illness with mevinphos or with application work. The exclusion of some cases and larger number of controls would, however, be expected to reduce the power of the study to detect significant differences between the two groups. A similar effect would also result from under-reporting of cases to the California registry. [60,61] This source of random misclassification would not explain the observed association between application exposure, mevinphos, and ChE-related illness.

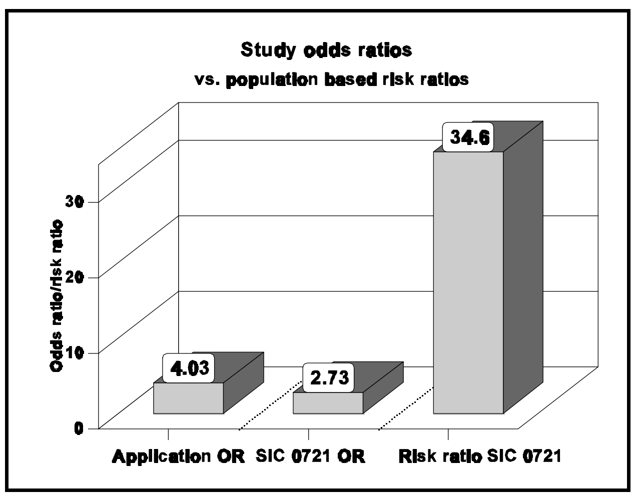

Figure 9 - odds ratios for application exposure and SIC 0721 (crop protection services) derived from the case-control study vs. population based risk ratios for ChE-illness and unemployment insurance SIC denominator data (Appendix 2)

Study OR vs population based risk ratios

Comparison of the OR calculated in this study for application exposures and for SIC 0721 (crop protection services) with risk ratios

(RR) computed from population based rates for ChE-related illness (Appendix 2) by person-years of employment for individual SIC categories risk ratio indicates that the study method may under estimate, rather than over estimate risk (Figure 9). The ChE-Illness rate (cases/10,000 person-years of employment) for crop protection services (SIC 0721, principally consisting of professional pesticide applicators) = 10,000*(131/37,877) = 34.6. This rate compares to the rate of 1.005 (265 cases/2,637,021 person-years of employment) for all other agricultural SIC categories combined. The relative risk for application work derived by comparing these separate rates is 34.6, approximately 9 times the OR of 4.03 for application exposure calculated from the crude logistic regression analysis in the case control study and the 3.81 OR calculated for SIC 0721. It cannot be ascertained from the existing data whether a similar negative bias may apply to the observed association between ChE-related illness and application related exposure to mevinphos. The majority (61.7%) of the application exposure to mevinphos occurred in the presence of other ChE inhibitors. The results of the multivariate analysis, nevertheless, indicate that mevinphos is a greater risk factor for ChE-illness (OR = 6.2) than the use of multiple ChE inhibitors (OR = 2.1).

Prior literature

The finding of an association between mevinphos and ChE-related illness is unsurprising, given the high vapor pressure of this compound, its extreme toxicity, and the long history of poisonings associated with its formulation[62,63] and use.[64,65,66,67,68,69,70,71,72,73] Although illnesses associated with mevinphos have been reported most frequently in California, reports from Australia,[74,75] Germany,[76] and Colorado,[77] as well as recent applicator poisonings in the state of Washington[78] and field worker poisonings in Florida,[79] indicate that occupational illnesses associated with mevinphos are not limited to California.

The ongoing poisonings with mevinphos have occurred despite institution of closed loading system requirements in California over the period 1972-1977.[80] Close to 50% of the ChE-illnesses associated with mevinphos application in California over the 1982-1990 period have occurred in applicators who reported complying with proper application procedures (including closed system requirements) and did not have any accidental direct exposure. Although the enforcement-oriented nature of the California illness investigation may prevent accurate disclosure of all violations that occur, poisonings associated with reported routine application occur with significantly greater relative frequency (OR = 8.4) in association with mevinphos than with other OP compounds.[81] An even greater relative frequency of ChE-illness is associated with violations of proper mevinphos application procedure (OR = 18.0).[82] These observations are in accord with the high toxicity of mevinphos on dermal application[83] and results of studies on human volunteers[84,85,86,87] (that formed the basis of the California Department of Pesticide Regulation (CDPR) 's risk characterization document[88]) demonstrating 25 µg/kg/day no-observed-effect-levels (NOELs) for cholinergic signs following exposure to mevinphos over 30 day intervals. The administration of mevinphos at this dose produced mild inhibition of both RBC and plasma ChE.[89] Because the range of exposures associated with closed mixing and loading systems is quite variable,[90] it is apparent the protection provided by these devices cannot be predicted with certainty when handling materials with high vapor pressures and low NOELs for cholinergic signs. The registrant of mevinphos voluntarily cancelled the registration in an agreement with and the U.S. Environmental Protection Agency in June 1994.

Conclusion

Among the principal categories of agricultural OP exposure, applicators had the highest risk of ChE-illness, despite the occurrence of significant field residue clusters throughout the study period. The largest number of both ChE and non-ChE illnesses were associated with mevinphos. Exposure to this compound was a highly significant risk factor for application association exposures and for field reentry violations. These study findings were unlikely to have been due to either random or non-random study bias. This study demonstrated that registry based case-comparison analysis can provide a useful alternative to the IPUR as a means of evaluating the comparative risk of OP compounds, allowing simultaneous examination of demographic factors, work tasks, and multiple insecticide exposures.

References

1. Maddy KT, Edmiston S, and Richmond D. Illnesses, injuries and deaths from pesticide exposures in California 1949-1988. **Rev Env Contam Toxicol** 1990 114:58-123

2. Pease WS, Morello-Frosch RA, Albright DS, Kyle AD, and Robinson JC: Preventing pesticide-related illness in California Agriculture, strategies and priorities. Berkeley, California, 1993. California Policy Seminar Report, University of California

3. ibid

4. United States Environmental Protection Agency. Questions and Answers: EPA effort to reduce acute health risks to agricultural workers from pesticides. April 1993. Washington D.C.

5. Weinbaum Z. Risk factors for agricultural restricted organophosphate OP-related systemic illnesses in California, 1984-1988. Davis, California 1994. Thesis Dissertation, Chapter 4, University of California, Davis

6. Kleinbaum DG, Kupper LL, and Morgenstern H: **Epidemiologic Research Principles and Quantitative Methods** Belmont California 1982, Lifetime Learning Publications

7. Lilienfeld AM and Lilienfeld DE. **Foundations of Epidemiology**. New York 1980. Oxford University Press. p. 209

8. Schlesselman JJ. **Case-control studies. Design, Conduct, and Analysis**. New York, 1982. Oxford University Press, pp. 25, 76-78, 134-135

9. Ames RG and Stratton JW. Acute health effects from community exposure to n-propyl mercaptan from an ethoprop (Mocap®)-treated potato field in Siskiyou County, California. **Arch Env Health**. 1991 46:213-217

10. Shusterman D. Critical review: the health significance of environmental odor pollution. **Arch Env Health** 1991 46:76-77

11. O'Malley M. Systemic illnesses associated with exposure to parathion in California, 1982-1989. January 1992 Sacramento, California. Cal EPA Department of Pesticide Regulation, Worker Health and Safety Branch, HS-1625

12. O'Malley M. Systemic illnesses associated with exposure to mevinphos in California, 1982-1989. January 1992 Sacramento, California. Cal EPA Department of Pesticide Regulation, Worker Health and Safety Branch, HS-1626

13. MacMahon B, Yen S, Trichopoulos D, Warren K, and Nardi G. Coffee and cancer of the pancreas. **N England J Med** 1981 304:630-633.

14. Burkman RT, Mason KJ, and Gold EB. Ectopic pregnancy and prior induced abortion. **Contraception**, 1988 37:21-27

15. Checkoway H, Pearce N, and Crawford-Brown DJ. **Research Methods in Occupational Epidemiology**. 1989 New York Oxford University Press pp 56-61

16. Gold EB, Gordis L, Diener MD, Seltser R, Boitnott JK, Bynum TE, and Hutcheon DF. Diet and other risk factors for cancer of the pancreas. **Cancer** 1985 55:460-467

17. van Leeuwen FE, Benraadt J, Coebergh JW, Kiemeney LA, Gimbrere CH, Otter R, Schouten LJ, Damhuis RA, Bontenbal M, Diepenhorst FW. et al. Risk of endometrial cancer after tamoxifen treatment of breast cancer. **Lancet** 1994 343:448-452

18. Weinstock MA. A registry-based case-control study of mycosis fungoides. **Ann of Epidemiology** 1991 1:533-539

19. Hallquist A, Hardell L, and Lofroth PO. External radiotherapy prior to thyroid cancer: a case-control study. **Int. J Rad Oncol Bio Physics** 1993 27:1085-1089

20. Office of Occupational Health Surveillance and Biometrics. National occupational hazard survey. 1974, Rockville, Md. Dept. of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health DHEW publication no. (NIOSH) 74-114, 74-127

21. Sieber WK. National occupational exposure survey : sampling methodology. Cincinnati, Ohio, 1990. U.S. Dept. of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, Division of Surveillance, Hazard Evaluations, and Field Studies. DHHS publication no. (NIOSH) 89-102

22. Rothman KJ. **Modern Epidemiology**. 1986 Boston Little Brown and Company. p 73

23. Bristle NE and Day NE. **Statistical Methods in Cancer Research.** Lyon 1987. International Agency for Cancer Research (ARC). ARC Scientific Publications No. 82

24. Rothman KJ. *op. cit*. p 73

25. Pesticide Annual Use Report by Chemical, 1990. Sacramento, California 1992 Cal EPA Department of Pesticide Regulation, Information Services Branch

26. O'Malley M Systemic Illnesses Associated with Exposure to Mevinphos in California, 1982-1989. January, 1992. Sacramento. California Department of Pesticide Regulation Worker Health and Safety Branch HS-1626

27. Office of management and budget, statistical policy division. **Standard Industrial Classification Manual, 1972.** Washington, D.C.

28. Office of management and budget, statistical policy division. **Standard Industrial Classification Manual, 1977 supplement.** Washington, D.C.

29. Office of management and budget, statistical policy division. **Standard Industrial Classification Manual.** Washington, D.C. 1987

30. Campos PV and Kotkin-Jaszi S. California farmworker enumeration report. Sacramento, California June 1987. Associated California Health Centers-California Health Federation

31. Vaupel S. Minorities and women in California agriculture. January 1988. Davis, California. Agricultural Issues Center, University of California

32. Employment Development Department. Agricultural employment pattern study: 1988. Sacramento, California

33. Mines R and Kearney M. The health of Tulare county farmworkers: a report of the 1981 survey and ethnographic research for the Tulare County Department of Health. April, 1982. San Diego and Riverside California. Tulare County Department of Health Services, University of California, San Diego, and University of California, Riverside

34. Alvarado AJ, Riley GL, and Mason HO. Agricultural workers in central California, Phase II, 1990-91. Fresno, California, 1992. California Agricultural Studies report. California Department of Employment Development, Sacramento, California and Center for Agricultural Business, California State University, Fresno

35. Mines R and Martin PL. A profile of California farmworkers. Davis, California 1986. Giannini Foundation of Agricultural Economics, University of California Davis. Giannini Information Series number 86-2

36. Mason HO, Alvarado AJ, and Riley GL . Agricultural workers in central California in 1989. Fresno, California, 1989. California Agricultural Studies report. California Department of Employment Development, Sacramento, California and Center for Agricultural Business, California State University, Fresno

37. U.S. Bureau of Labor Statistics. Employment and Wages, Annual Averages. Washington, D.C., 1990, 1989, 1988, 1987, 1986, 1985, 1984, 1983, 1982

38. Pesticide Annual Use Report by Chemical, 1990. Sacramento, California 1992 Cal EPA Department of Pesticide Regulation, Information Services Branch

39. Norusis MJ: **SPSS/PC+ Base Manual**. Chicago: SPSS Inc. 1990

40. Norusis MJ, *op. cit.*

41. O'Malley M. Investigation of a death by ingestion of parathion in the Lost Hills area of Kern County, California, January 20, 1990. Sacramento 1993. Cal EPA Department of Pesticide Regulation, Worker Health and Safety Branch, publication HS-1667

42. Osorio AM, Ames RG, Rosenberg J, and Mengle DC. Investigation of a fatality among parathion applicators in California. Am J Ind Med 1991 20:533-546

43. Ames RG and Stratton JW, 1991 *op cit*

44. Shusterman D, 1991 *op. cit.*

45. Executive summary of 1980 DEF and butyl mercaptan monitoring study. Sacramento 1981 Environmental Monitoring and Pest Management, California Department of Food and Agriculture

46. Environmental Hazards Assessment Program. Drift studies from the aerial application of DEF and folex in Fresno and Merced counties, California 1979. Sacramento 1980. Environmental Monitoring and Pest Management, California Department of Food and Agriculture

47. Thongsinthusak T, Brodberg RK, Dong MH, Haskell D, Ross JH, and Sanborn JR. Estimation of exposure to persons in California to pesticide products that contain chlorpyrifos. Cal EPA Department of Pesticide Regulation Publication HS-1661

48. Royal Society of Chemistry. **Agrochemicals Handbook**. Nottingham, 1986

49. Maddy KT, Edmiston S, and Richmond D. 1990, *op. cit.*

50. O'Malley M and McCurdy S. Subacute poisoning with the organophosphate insecticide, phosalone. **West J Med**. 1990 153:619-624

51. Midtling JE, Barnett PG, Coye MJ, et al. Clinical Management of Organophosphate poisoning. **West J Med**. 1985 142:514-518

52. Richards DM, Kraus JF, Kurtz P, and Borhani NO. A controlled field trial of physiological responses to organophosphate residues in farm workers. **J Env Path Toxicol** 1978 2:493-512

53. Kraus JF, Richards DM, Borhani NO, Mull R, Kilgore WW, and Winterlin W. Physiological response to organophosphate residues in field workers. **Arch Env Contam Toxicol** 1977 5:471-485

54. Kraus JF, Mull R, Kurtz P, Winterlin W, Franti CE, Kilgore W, and Borhani NO. Monitoring of grape harvesters for evidence of cholinesterase inhibition. **J Toxicol Env Health** 1981 7:19-31

55. Kraus JF, Mull R, Kurtz P, Winterlin, Franti CE, Borhani N, and Kilgore W. Epidemiologic study of physiological effects in usual and volunteer citrus workers from organophosphate pesticide residues at reentry. **J Toxicol Env Health** 1981 8:169-184

56. Knaak JB, Maddy KT, Jackson T, Fredrickson AS, Peoples SA, and Love R. Cholinesterase activity in blood samples collected from field workers and non field workers in California. Sacramento, California 1978. Worker Health and Safety Unit, California Department of Food and Agriculture. HS-561

57. Maddy KT, Edmiston S, Rech C, and Margetich S. A survey of selected vineyards and orchards at harvest for dislodgeable foliar organophosphate pesticide residues in Sonoma and Santa Cruz Counties 1985. Sacramento, California 1986. Worker Health and Safety Unit, California Department of Food and Agriculture. HS-1362

58. Maddy KT, Smith CR, Kilgore SL, Alcoser D and Brittain Y. A survey of dislodgeable organophosphate residues in San Luis Obispo, Santa Barbara, and Ventura Counties at the time of harvest during the spring of 1985. Sacramento, California 1986. Worker Health and Safety Unit, California Department of Food and Agriculture. HS-1348

59. Knaak JB, Maddy KT, and Khalifa S. Alkyl phosphate metabolite levels in the urine of field workers giving blood for cholinesterase test in California. **Bull Environ Contam Toxicol** 1979 21:375-380

60. Kahn E. Pesticide related illness in California Farmworkers. **J Occup Med**. 1976 18:603-606

61. Peoples SA, Maddy KT, and Smith CR. An overview of occupational exposures to pesticides in 1981. Sacramento, California: California Department of Food and Agriculture, Worker Health and Safety Branch, 1982. Publication HS-985

62. Peoples SA, Maddy KT, and Edmiston S. Human health problems associated with mevinphos (Phosdrin) in California 1975-1977. Sacramento, 1978. California Department of Food and Agriculture, Worker Health and Safety Branch. Publication HS-373

63. Roche L, Le Jeune E, and Madonna RJM. Four poisonings with phosdrin. **Arch Mal Prof Med Trav Secur Soc** 1961 22:52-55

64. *ibid.*

65. Midtling JE, Barnett PG, Coye MJ, et al: Clinical management of field worker organophosphate poisoning. **West J Med** 1985 142:514-518

66. Romero P, Barnett PG, and Midtling JE. Congenital anomalies associated with maternal exposure to oxydemeton-methyl. **Environmental Research**, 1989 Dec, 50:256-261

67. Coye MJ, Barnett PG, Midtling JE, Velasco AR, Romero P, Clements CL, and Rose TG. Clinical confirmation of organophosphate poisoning by serial cholinesterase analyses. **Archives of Internal Medicine**, 1987 Mar, 147:438-42

68. Maddy KT, Smith C, and Updike D. Occupational exposures to mevinphos (Phosdrin) reported by physicians in California during 1980. Sacramento, 1981. California Department of Food and Agriculture, Worker Health and Safety Branch. Publication HS-873

69. Midtling JE, Barnett PG, Coye MJ, et al: Clinical management of field worker organophosphate poisoning. **West J Med** 1985 142:514-518

70. Maddy KT, Richmond D, and Updike D. Human health problems associated with mevinphos (Phosdrin) in California during 1979. Sacramento, 1981. California Department of Food and Agriculture, Worker Health and Safety Branch. Publication HS-836

71. Maddy K and Christiansen R. Human health problems associated with mevinphos (Phosdrin) in California during 1978. Sacramento, 1979. California Department of Food and Agriculture, Worker Health and Safety Branch. Publication HS- 667

72. Brachfield J and Zavon MR. Organic phosphate (phosdrin) intoxication. Report of a case and the results of treatment with 2-PAM. **Arch Env Health** 1965 11:859-862

73. Gonzalez-Laprat JA, Migliaro JP, Ferrari-Fourcade A, Saavedra M, and Tugentman A. Intoxication with organophosphate inhibitors of cholinesterase. Three cases of accidental simultaneous accidental intoxication with with phosdrin. **An Fac Med Montevideo** 1966 50:255-268

74. Simpson GR and Penney DJ. Pesticide poisonings in the Namoi and Macquarie Valleys, 1973. **Med J Australia** 1974 1:258-260

75. Sagerser C, Skeers V, Baum L, Magaña M, Morrisey B, Mason B, and Kobayashi JM. Occupational pesticide poisoning in apple orchards - Washington, 1993. **MMWR** 1994 **42**:993-995

76. Stoeckel H and Meinecke KH. On a case of occupational poisoning by Mevinphos. **Archiv fur Toxikologie**, 1966 21:284-8

77. Holmes JH, Starr HG Jr, Kaulla KN von, and Hanisch RC. Short-term toxicity of mevinphos in man. **Arch Environ Health**, 1974 29:84-9

78. Sagerser C, Skeers V, Baum L, Magaña M, Morrisey B, Mason B, and Kobayashi JM. Occupational pesticide poisoning in apple orchards - Washington, 1993. **MMWR** 1994 **42**:993-995

79. Baer RAD and Penzell D. Research report: Susto and pesticide poisoning among Florida farmworkers. Culture, Medicine, and Psychiatry. 1993 17:321-327

80. Rutz R. Closed system acceptance and use in California in **Pesticide Formulations and Application Systems: Seventh Volume.** Philadelphia 1987, GB Beestman and DIB Vander Hooven, Eds. American Society for Testing Materials publication, pp 28-34

81. O'Malley M. Addendum Report: Mevinphos illness cases 1982-1990 compared to other organophosphate insecticides Sacramento, 1993 Cal EPA Department of Pesticide Regulation Worker Health and Safety Branch publication HS-1626A

82. *ibid.*

83. Gaines TB. Acute toxicity of pesticides. **Toxicol App Pharmacol** 1969 14:515-534

84. Verbek MM and Salle HJ. Neurological effects and cholinesterase inhibition in man by subacute administration of mevinphos. **Activitas Nervosa Superior**, 1979 Suppl 2:333-334

85. Verberk MM. Incipient cholinesterase inhibition in volunteers ingesting monocrotophos or mevinphos for one month. **Toxicol and App Pharmacol** 1977 42:345-50.

86. Verberk MM and Salle HJ. Effects on nervous function in volunteers ingesting mevinphos for one month. **Toxicol and App Pharmacol** 1977 42:351-8

87. Rider JA, Puletti EJ, and Swader JI. The minimal oral toxicity level for mevinphos in man. **Toxicol and App Pharmacol** 1975 32:97-100

88. Cochran R. Mevinphos (Phosdrin®) risk characterization document. June, 1994. Medical Toxicology and Worker Health and Safety. California Department of Pesticide Regulation.

89. Verberk MM and Salle HJ. Effects on nervous function in volunteers ingesting mevinphos for one month. **Toxicol and App Pharmacol**, 1977 42:351-8

90. Rutz R and Krieger R. Exposure to pesticide mixer/loaders and applicators in California. **Rev Env Contam Toxicol** 1992 129:121-139

Table 1 Demographic and Illness characteristics of Cases, Controls, and Excluded Subjects									
Variable	**Cases n = 396**	**%**	**Controls n = 758**	**%**	**Excluded n = 562**	**%**	**Total n = 1,716**	**%**	**Ag Population values**
Demographic variables									
Males	347	87.6	579	76.5	465	82.7	1391	81.1	70%[d], 51-93%[e]
Females	49	12.4	179	23.6	97	17.3	325	18.9	30%, 7-49%
Hispanic	293	74.0	657	86.7	438	77.9	1388	80.9	61.4-89.7%[f]
Mean age	29.4		31.6		29.6		30.9		30.5
Employment variables									
Crop Production SIC codes	179	45.2	526	69.4	326	58.0	1031	60.1	44.9
Livestock SIC codes	2	0.5	2	0.3	11	2.0	15	0.9	10.4
Service SIC codes	215	54.3	230	30.3	225	40.0	670	39.0	44.7
Illness Characteristics									
Cluster Episodes	173	43.7	515	67.8	225	40.0	913	53.2	na
Non-specific symptoms compatible with ChE-illness	396	100.0	575	75.9	470	83.6	1441	84.0	na
Specific Symptoms	167	42.2	na	na	2	0.4	82	4.8	na
Odor	80	20.2	370	48.8	123	21.9	573	33.4	na
Irritant Symptoms	114	28.8	263	34.7	165	29.4	542	31.6	na
Hospitalized	104	27.1	16	2.2	20	3.6	140	8.2	na
Disability	213	69.2	267	42.6	205	36.5	685	39.9	na

---

d Vaupel S. Minorities and women in California agriculture. January 1988. Davis, California. Agricultural Issues Center, University of California

e Mason HO, Alvarado AJ, and Riley GL . Agricultural workers in central California in 1989. Fresno, California, 1989. California Agricultural Studies report 91-5. California Department of Employment Development, Sacramento, California and Center for Agricultural Business, California State University, Fresno

f Mason HO, Alvarado AJ, and Riley GL . Agricultural workers in central California in 1989. Fresno, California, 1989. California Agricultural Studies report 91-5. California Department of Employment Development, Sacramento, California and Center for Agricultural Business, California State University, Fresno

Table 2 - Differences among cases controls and excluded subjects by ChE activity													
Type of ChE Information Available	**Cases n = 396[g]**	**%**	**Median RBC Depres-sion**	**Median Plasma Depres-sion**	**Con-trols n = 758**	**%**	**Median RBC Depres-sion**	**Median Plasma Depres-sion**	**Exclu-ded n = 562**	**%**	**Median RBC Depres-sion**	**Median Plasma Depres-sion**
ChEclass = 1.0 or 1.1; RBC/plasma ChE Reported normal	9	2.3	na	na	187	24.7	na	na		1.1	na	na
ChEclass = 2.0; RBC/Plasma ChE reported depressed	26	6.6	na	na	0	0	na	na	31	5.5	na	na
ChEclass = 3.0 or 5.0; No test done/no results available	57	14.4	na	na	80	10.6	na	na	463	82.4	na	na
ChEclass = 4.0; ChE within population normal range	19	4.8	0.0	0.0	466	61.5	0.0	0.0	8	1.4	0.0	0.0
ChEclass = 4.1; ChE below population normal range	223	56.3	45.3	59.1	0	0.0	na	na	40	7.1	45.7	0.0
ChEclass = 4.2; baseline ChE available	42	10.6	48.8	61.7	19	2.5	2.0	1.3	10	1.8	20.9	1.9
ChEclass = 4.3; followup ChE samples available	9	2.3	22.0	20..0	0	0.0	na	na	3	0.5	24.8	32.0
ChEclass = 4.4;	11	2.8	na	45.2	6	0.8	0.0	0.0	1	0.2	0.0	0.0

[g] 5 additional cases excluded because OP compound was unknown

Table 3 Crude odds ratios for individual exposure related variables								
VARIABLE	**Exposure variable present**			**Exposure variable not present**			**Statistical comparison**	
	Cases	**Non-cases**	**Total**	**Cases**	**Non-cases**	**Total**	**Odds ratio**	**p-value**
Activity and employment variables								
Drift	51	416	467	345	342	687	0.12	< 10-5
Application	202	154	356	194	604	798	4.08	< 10-5
Direct exposure	74	25	99	322	733	1055	6.74	< 10-5
Routine application	97	115	212	299	643	942	1.81	1.4x10-4
Violation of application procedure	31	14	45	365	744	1109	4.51	< 10-5
Field Residue	118	148	266	278	610	888	1.75	1.1x10-4
Normal field reentry	82	108	190	314	650	964	1.57	6.42x10-3
Field reentry violation	36	40	76	360	718	1078	1.80	1.9x10-2
Ingestion	4	2	6	392	756	1148	3.86	0.19f
Crop production SIC code	179	526	705	217	232	449	0.36	< 10-5
Agricultural Service SIC code	215	230	445	181	528	709	2.73	< 10-5

Table 3 Crude odds ratios for individual exposure related variables

VARIABLE	Exposure variable present			Exposure variable not present			Statistical comparison	
	Cases	Non-cases	Total	Cases	Non-cases	Total	Odds ratio	p-value
Crop protection services - SIC 0721	131	87	218	265	671	936	3.81	< 10-5
Chemical exposure variables								
Mevinphos	158	337	495	238	421	659	0.83	0.15
Methomyl	88	123	211	308	635	943	1.48	0.015
Oxydemeton-methyl	71	142	313	325	516	841	0.79	< 10-5
Parathion	55	93	148	341	665	1006	1.15	0.49
Phosalone	51	11	62	345	747	1092	10.04	< 10-5
Dimethoate	39	178	217	357	580	937	0.36	< 10-5
Metham-idophos	37	185	222	359	573	932	0.32	< 10-5
Diazinon	35	31	66	361	727	1088	2.27	1.55x10-3
Chlorpyrifos	24	52	76	372	706	1078	0.88	0.69
Azinphos-methyl	14	34	48	382	724	1106	0.78	0.54
Methida-thion	12	28	40	384	730	1114	0.81	0.68

Table 3 Crude odds ratios for individual exposure related variables								
VARIABLE	Exposure variable present			Exposure variable not present			Statistical comparison	
	Cases	Non-cases	Total	Cases	Non-cases	Total	Odds ratio	p-value
Demeton	10	5	15	386	753	1139	3.90	0.017

Table 4 Stratum specific odds ratios for individual chemical exposures

VARIABLE	Exposure variable present			Exposure variable not present			Statistical comparison	
	Cases	Non-cases	Total	Cases	Non-cases	Total	Odds ratio	p-value
Application related cases (n = 356)								
Acephate	4	17	21	198	137	335	0.16	7.6x10-4
Mevinphos	88	14	102	114	140	254	7.72	< 10-5
Methamido-phos	19	5	24	183	149	332	3.09	3.7x10-2
Methomyl	49	12	61	153	142	295	3.79	8x10-5
Parathion	26	44	70	176	110	286	0.37	3.7x10-4
Multiple category 1 ops	35	7	42	167	147	314	4.40	4.0x10-4
Multiple ChE inhibitors	93	32	125	109	122	231	3.25	< 10-5
Field residue related exposures (n = 275)								
Mevinphos	31	14	45	87	134	221	3.41	5.2x10-4
Oxydemeton-methyl	36	28	64	82	120	202	1.88	4.0x10-2
Phosalone	51	10	61	67	138	205	10.50	< 10-5

Table 4 Stratum specific odds ratios for individual chemical exposures								
VARIABLE	**Exposure variable present**			**Exposure variable not present**			**Statistical comparison**	
	Cases	**Non-cases**	**Total**	**Cases**	**Non-cases**	**Total**	**Odds ratio**	**p-value**
Multiple category 1 ops	32	6	38	86	142	228	8.81	< 10-5
Acephate	2	22	24	116	126	242	0.10	4.5x10-4
Dimethoate	5	27	32	113	121	234	0.20	9.7x10-4
Azinphos-methyl	4	22	26	114	126	240	0.20	3.5x10-3

Table 5 - Results of Logistic Regression Analysis for Application exposures		
Logistic regression of application exposures (n=356)		
Hispanic	1.8	0.02
Mevinphos	6.2	< 10-5
Multiple ChE inhibitors	2.1	0.005
Tested variables not retained in the model by the stepwise procedure included sex, age-range, methamidophos exposure, melthomyl exposure, and exposure to multiple category 1 OPs.		

Table 6 - Field residue associated cluster episodes

Id	Pesticides	# Cases	# Controls	Comment
1523-82	Parathion	15	7	Picking in block sprayed 35 days earlier with parathion; ate lunch & rested in block sprayed 27 days before the episode.
2095-82	Mevinphos Methomyl Not determined	29	2	Crew foreman permitted crew to enter a cauliflower field 24 hours after application. Reentry interval was three days and field was posted.
1439-83	Parathion	0	2	Working on irrigation pump in vicinity of parathion treated orchard.
1421-85	Parathion	4	0	Picking grapefruit in grove sprayed with parathion 47 days prior to picking. High levels of parathion in duff (dead leaves) under trees.
381-83	Oxydemeton-methyl Dimethoate	4	18	Field was treated 4/5/83, then posted. Signs were knocked down 4/6 by fertilizer rig. Crew entered field about 24 hours early.
1450-85	Parathion	0	4	Several members of the crew had drift exposure to parathion; several had residue exposure immediately following the application.
1250-86	Propargite Methamidophos	0	9	Workers ran into a treated field to escape from border patrol.
1405-86	Acephate Maneb Metalaxyl	1	12	A group of workers thought they were exposed to OPs when they found a posting sign in a corner of the field and they sought medical treatment 1-1.5 weeks later.
1621-87	Azinphos-methyl Methomyl Not determined	1	21	Thirty-six workers entered a field to pick peaches 3 days after a methomyl application & about 6 weeks after a azinphos-methyl application. Adjacent fields were also treated. Residue was below the safe reentry levels for both pesticides.
1815-87	Phosalone	12	1	Picking wine grapes, persistent phosalone residues found in vineyard 30+ days after application..
1850-87	Triadimefon Phosalone	19	1	While picking, developed flu-like symptoms. Entire crew had depressed ChE levels. No violations of reentry interval noted.
1918-87	Phosalone	18	0	Picking wine grapes, persistent phosalone residues found in the vineyard one hundred days after application
2162-87	Phosalone	1	8	Harvesters exposed to phosalone while hand-harvesting grapes. All workers were supplied with protective clothing and baseline ChE tests. One had significant decrease from baseline test, approximately 21%.
6318-88	Acephate	1	6	Seven workers in a crew of disbudders became ill after 2 1/2 hours of work. Acephate applied 13 hours earlier. ChE compatible and irritant symptoms reported.

Index case ID	Pesticides	# Cases	# Controls	Comment
637-84	Mevinphos	15	4	Drift incident involving lettuce harvesting crew.
692-89	Chlorpyrifos Adjuvant		25	Crew of field workers drifted on by an adjacent application.
771-85	Mevinphos Naled Vinclozolin		23	Worker allegedly contacted drift from nearby aerial pesticide application. ChE levels within normal population range.
1006-83	Naled		6	Exposed to drift but no symptoms. Six employees involved.
1297-83	Oxydemeton-methyl Dimethoate Mevinphos	4	120	Harvesters 1/8 mile from aerial application developed symptoms and emotional distress after smelling foul odor and observing helicopter. Field supervisor sent all to hospital after working 15 minutes in the field.
1450-85	Parathion		10	Because of miscommunication, an irrigator and several field workers were drifted upon by an aerial application. Other field workers entered the field immediately after the application and had principally residue exposure.
1470-84	Methomyl Maneb Mevinphos		38	Possible mevinphos, methomyl and maneb drift exposure. Began working in field adjacent to a field treated with mevinphos an hour earlier. Crew members complained of odor. Residue samples taken 12 hours later showed ppm levels of mevinphos.
1509-86	Methidathion		14	Drift onto pickers from nearby citrus application.
1625-87	Malathion		4	Four workers were possibly exposed to malathion while walking in a field adjacent to the one being sprayed. They were also very nervous about the pesticides being applied.
1644-83	Mevinphos Methamidophos	1	23	Harvesters working 3/4 mile from aerial application, 6 developed symptoms after detecting a foul odor.
1679-86	Naled Sulfur	2	2	Greenhouse worker became ill after they smelled an odor from a pesticide application on a nearby strawberry field.
2117-84	Methomyl Permethrin Maneb	1	8	Workers became ill while harvesting green onions near an application of multiple ChE inhibitors to a lettuce field.
2175-82	Oxydemeton-methyl Mevinphos Dithane	7	13	Thinning crew was drifted on by aerial application one eighth of a mile away.
2372-85	Mevinphos	3	44	Two aerial applications were performed within a mile of a lettuce harvesting crew. Most of the crew was symptomatic.

Table 7 - Drift cluster episodes

Table 7 - Drift cluster episodes				
Index case ID	**Pesticides**	**# Cases**	**# Controls**	**Comment**
2756-87	Fenvalerate Mevinphos		23	Workers harvesting/tying cauliflower could smell the odor (drift) from a nearby application to artichokes. The application was 100-200 yds. away.

Appendix 1 - Classification of symptoms, exposures, ChE data and ChE-illnesses

Classification of symptoms

Signs and symptoms associated with each case were reviewed in two stages in order to determine whether the clinical findings were compatible with systemic organophosphate poisoning and if so whether any specific signs or symptoms (i.e., those not usually found in common nonoccupational illnesses) were present. Within the data entry program, a partial list of compatible and specific symptoms was included to facilitate the review of medical records by a data entry technician.

SIGNS/SYMPTOMS COMPATIBLE WITH OP POISONING: diarrhea, salivation, urination, sweating, abdominal pain, dizziness, headache, nausea, blurry vision, dyspnea, etc[h]
ENTER REPORTED SYMPTOMS:

Are reported symptoms compatible? 1 = yes 2 = no 3 = unspecified 4 = no symptoms

Are SPECIFIC SIGNS/SYMPTOMS (miosis, salivation, sweating, involuntary urination, lacrimation, or bradycardia) present? 1 = yes 2 = no 3 = unspecified

Irritant symptoms were coded based on the reported presence of "irritation", "soreness" or "burning" of the chest, throat, eyes, or skin. Also coded as irritant symptoms were reported episodes of paresthesias or tingling of the skin, and overt skin reaction following the reported exposures.

Classification of exposure

Exposures were categorized to define possible means of preventing the reported illnesses, recognizing that confirmed cases of poisoning occurring despite reported compliance with mandated safety precautions are of special regulatory significance. Below is a listing of the codes used by CDPR since 1989 for categorizing exposures to all carbamate or organophosphate compounds, in both agricultural and non-agricultural settings:

1 = direct eye/skin exposure during application/spill - i.e. direct contact with pesticide. No explicit distinction within this category is made based upon the amount of contact.
2.0 = exposure from outdoor drift/spill - usually inhalation or spray droplet exposure resulting from a distant application or spill
2.1 = present in field at time of pesticide application
3 = dermal/respiratory exposure after indoor spill - similar to category 2 except for location of spill. Not usually applicable to the use of agricultural OPs.
4 = vapors/odors from normal indoor application. Not usually applicable to use of agricultural OPs.
5.0 = fieldwork with normal reentry. Exposure to field residue of OPs. Compliance with existing waiting period for field reentry.
5.1 = field reentry prior to expiration of reentry interval, limited exposure - e.g. reentry to perform irrigation work
6 = violation of field reentry interval. Entry into a treated field prior to expiration of reentry interval.
7 = normal application work/no spill. No recorded violation of existing respiratory protection, closed system requirements, or other violations of regulatory requirements.
8 = failure to use closed system/respirator/other violation documented by illness investigation.
9.0 = residue ingestion
9.1 = deliberate or accidental ingestion of pesticide concentrate or tank mix
10 = other miscellaneous category includes exposures resulting from pesticide fires, cleaning and repairing of application equipment, except where an accidental direct exposure occurred.
11 = No evidence of exposure

---

h The data entry program did not attempt to list of all possible symptoms of organophosphate/carbamate poisoning, but focused on those most commonly found in PISP records. For a listing see: Morgan DP. The Recognition and Management of Pesticide Poisoning, Fourth Edition. Washington D.C.: United States Environmental Protection Agency. Office of Pesticide Programs: March 1989. Publication EPA-540/9-88-001). Signs and symptoms judged as relatively specific for OP poisoning by the author are as listed.

Classification of ChE data (ChEclass codes)

1 = reported normal in the medical record or county pesticide episode investigation report specific values not recorded
2 = reported depressed, specific values not recorded
3 = no test ordered or unspecified
4.0 = test results available, results indicate both RBC and plasma ChE are greater than the lower limits of the normal range for the lab running the assay.
4.1 = test results available, results indicate either or both RBC and plasma ChE are less than the lower limits of normal range for the lab running the assay.
4.2 = test results available for date of illness and also a comparison baseline test- % depression calculated for both RBC and plasma ChE versus midpoint of baseline
4.3 = test results available for date of illness and also a comparison followup test- % depression calculated for both RBC and plasma ChE versus followup tests
4.4 = lower limit of normal specified only % depression calculated versus lower limit.
5 = ChE test ordered/ results not available

Classification of illness

Definite Cases - One or more compatible symptoms, accompanied by at least a 20% decrease in plasma and/or RBC ChE from non-exposed to exposed blood samples. In the absence of data from paired samples, an RBC ChE or plasma ChE value below the specified normal range was taken as evidence of definite illness, if accompanied by compatible symptoms. Cases with compatible symptoms accompanied by a qualitative report of depressed ChE were also taken as definite cases.

Probable Cases - ChE data missing or ambiguous, compatible signs/symptoms accompanied by relatively specific signs/symptoms as defined above.

Possible Cases - Compatible symptoms only - ChE information missing or not definitive - including samples in the normal range for which no comparison samples were available.

Unlikely - Compatible symptoms, but ChE data are negative based upon either baseline or followup samples.

Unrelated - Definite alternative diagnosis established.

Non-ChE effect - Reported irritant symptoms following exposure to OP in absence of symptoms compatible with ChE effect

Asymptomatic exposure - No reported symptoms following reported exposure.

Appendix 2 Cases vs controls vs excluded by SIC code OPCC8 study appendix 1						
SIC Description	**SIC#**	**Cases**	**Controls**	**Excluded**	**1982-1990 Population**	**ChEIllnesses/ 10,000 employed**
Wheat	0111	1			2006	4.99
Rice	0112		2	1	13985	0.00
Corn	0115			2	3746	0.00
Soybeans	0116				4696	0.00
Cash grains,NEC	0119		3	2	13167	0.00
All Grains	011	1	5	5	37600	0.27
Cotton	0131	4	19	39	65355	0.61
Tobacco	0132					
Sugar crops	0133		3	1	3067	0.00
Irish potatoes	0134	1		2	6307	1.59
Field crops, exc grains,NEC	0139	2		2	39354	0.51
All 013 Crops	013	3	3	5	48728	0.62
Vegetables & melons	0161	42	336	91	335774	1.25
Berry crops	0171	3	3	6	106345	0.28
Grapes	0172	64	48	47	316316	2.02
Tree nuts	0173		34	28	62110	1.77
Citrus	0174	9	14	18	59547	1.51
Deciduous tree fruit	0175	12	18	22	138403	0.87
Fruits and tree nuts, etc	0179		1	4	114752	0.00
All 017 Crops	017	88	118	125	797473	1.10
Ornamental nursery, etc	018	18	38	42	288602	0.62
General farms prim. crop	0191	12	7	19	302220	0.40
Non-dairy livestock	0200-0219			1	52334	
Dairy	0241	2		3	114564	0.17
Poultry	025		2	4	65652	0.00
Other livestock	0271-0291			3	30125	0.00
All livestock	02	2	2	11	262675	0.08

Appendix 2 Cases vs controls vs excluded by SIC code OPCC8 study appendix 1						
SIC Description	**SIC#**	**Cases**	**Controls**	**Excluded**	**1982-1990 Population**	**ChEIllnesses/ 10,000 employed**
Soil preparation services	0711		2	2	9932	0.00
Crop planting & protection services	0721	131	87	119	37877	34.59
Crop harvesting services	0722	22	81	28	62884	3.50
Crop preparation services	0723	18	42	20	223204	0.81
Cotton ginning	0724			2	14510	
General crop services	0729				5760	0.00
Vet services	0742	6	2	7	114201	0.53
Livestock services, exc. spec	0751	1			8462	1.18
Animal specialty services	0752			1	45990	0.00
Farm lab contractors	0761	35	13	25	538623	0.65
Farm management services	0762			1	93238	0.00
Hort/lands services	078	2	3	20	353458	0.06
All ag services	07	215	230	225	1508139	1.43
Forestry	08				10128	0.00
Fishing, hunting, trapping	09				18204	0.00
1982-1990 Population for represented SICs	01-09	3113502	3225474	3626204	3675882	0.00
% of total population		84.70	87.75	98.65	100.00	

Appendix 3 OP/carbamate use data and total number of study in 1982-90 study period for cases, controls and excluded subjects					
Pesticide	**1982-90 CASES**	**1982-90 Controls**	**1982-90 Excluded**	**1990 Applications**	**1990 Pounds Used**
Acephate	6	42	51	26248	403506.55
Aldicarb		2		6356	473296.05
Azinphos-methyl	14	34	49	8841	516870.49
Bendiocarb			1	1361	3297.7871
Bensulide			1	1079	64121.037
Bomyl				1	0.12
Carbaryl	9	5	7	14830	954280.66
Carbofuran	2		1	7703	345063.67
Carbophenothion				28	340.4469
Chlorpyrifos	24	52	57	46089	1860088.7
Coumaphos	1			2	0.2713
Crotoxyphos			1	1	13.241
DDVP	2	4	11	20987	1019.8723
DEF®	2	1	8	6511	1007013
Demeton	10	5	4	543	5399.4857
Diazinon	35	31	40	37954	899848.54
Dicrotophos				74	518.4144
Dimethoate	39	178	71	33873	879177.16
Dioxathion				21	10.8941
Disulfoton	7	1	3	4781	187903.36
Ethion	4	1		126	5267.9239
Ethoprop			2	248	38363.713
Famphur				1	0.02
Fenamiphos	2		1	2396	151522.53
Fensulfothion				1	4.3911
Fenthion	1		1	140	1858.3503
Fonofos			1	1556	7755.6215
Formetanate hydrochloride	1	3	2	8640	307505.97
Malathion	9	27	38	14760	1691846.5
Merphos	4		2	362	28913.438

Appendix 3 OP/carbamate use data and total number of study in 1982-90 study period for cases, controls and excluded subjects					
Pesticide	**1982-90 CASES**	**1982-90 Controls**	**1982-90 Excluded**	**1990 Applications**	**1990 Pounds Used**
Methamidophos	37	185	61	7416	409777.4
Methidathion	12	28	14	6335	351944.13
Methiocarb				1872	5476.8529
Methomyl	88	123	36	40452	881688.24
Methyl parathion	1	6	4	4670	106712.16
Mevinphos	158	337	93	49936	333793.15
Monocrotophos	2	2	1	20	109.7745
Naled	5	40	10	7046	449164.14
Oxamyl	1	2	2	4647	50478.121
Oxydemeton-methyl	71	242	31	15139	168378.15
Parathion	55	93	58	18640	755216.23
Phorate	2	7	5	2268	125750.19
Phosalone	51	11	30	319	14127.334
Phosmet	7	6	7	6014	257220.37
Phosphamidon		1	1	1240	38833.267
Profenofos	6	3	5	1965	17588.567
Propetamphos	1		1	139	248.5434
Propoxur				108	254.1808
Sulprofos			1	0	0
Temephos				18	5.3349
Tetrachlorvinphos			2	283	15102.901
Thiodicarb				2	2.1483
Trichlorfon		1	2	504	11845.959
Unknown			5	na	na
Total applications represented	399792	397150	405936	414546	416032
% of Total applications	96.44	96.44	96.44	100.00	100.00

Appendix 4 Application cases, application controls, total cases, and total controls from study period compared to 1990 use data for compounds associated with 10 or more study subjects											
Pesticide	**1982-90 App. ChE Illnesses**	**1982-90 App. Non-ChE Illnesses**	**Total Che Illnesses**	**Total Non-ChE-Illnesses**	**1990 Applications**	**App. Cases/ 10,000 App.**	**App. Control/ 10,000 App**	**Total App. Subjects /10,000**	**Total Cases/ 10,000 App.**	**Total Control/ 10,000 App**	**Total study subjects /10000**
Acephate	4	17	6	42	26248	1.5	6.5	8.0	2.3	16.0	18.3
Azinphos-methyl	7	9	14	34	8841	7.9	10.2	18.1	15.8	38.5	54.3
Carbaryl	8	4	9	5	14830	5.4	2.7	8.1	6.1	3.4	9.4
Chlorpyrifos	19	13	24	52	46089	4.1	2.8	6.9	5.2	11.3	16.5
Demeton	10	3	10	5	543	184.2	55.2	239.4	184.2	92.1	276.2
Diazinon	24	15	35	31	37954	6.3	4.0	10.3	9.2	8.2	17.4
Dimethoate	23	16	39	178	33873	6.8	4.7	11.5	11.5	52.5	64.1
Malathion	7	6	9	27	14760	4.7	4.1	8.8	6.1	18.3	24.4
Methami-dophos	19	5	37	185	7416	25.6	6.7	32.4	49.9	249.5	299.4
Methidathion	11	10	12	28	6335	17.4	15.8	33.1	18.9	44.2	63.1
Methomyl	49	12	88	123	40452	12.1	3.0	15.1	21.8	30.4	52.2
Mevinphos	88	14	158	337	49936	17.6	2.8	20.4	31.6	67.5	99.1
Naled	2	4	5	40	7046	2.8	5.7	8.5	7.1	56.8	63.9
Oxydemeton-methyl	19	11	71	242	15139	12.6	7.3	19.8	46.9	159.9	206.8
Parathion	26	44	55	93	18640	13.9	23.6	37.6	29.5	49.9	79.4
Phosalone	0	1	51	11	319	0.0	31.3	31.3	1598.7	344.8	1943.6
Phosmet	7	1	7	16	6014	11.6	1.7	13.3	11.6	26.6	38.2
Median value	11	10	24	40	14,830	7.9	5.7	15.1	15.8	44.2	63.1

The 17 compounds shown accounted for 334,435 total applications, 80.7% of the total for 1990.